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EXAMINER	
ROMEO, DAVID S	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/060,294	JENSEN ET AL.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/21/2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-132* is/are pending in the application.

4a) Of the above claim(s) *98-103,107-109,111-116,123,125 and 126* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-97,104-106,110,117-122,124 and 127-132* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *77-132* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 77-132 are pending.

Applicant's election of group I in the paper filed 10/21/2003 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant's election with traverse of the species E/F loop substitution in the paper filed 10/21/2003 is acknowledged. The traversal is on the ground(s) that the substitution in the E strand and in the E/F connecting loop species and the substitution in the E strand and in the E/F and D/E connecting loop species should also be examined with the elected species. This is found persuasive.

The requirement is still deemed proper and is therefore made FINAL.

Claims 82-84, 86, 98-103, 107-109, 111, 115, 116, 123, 125-127, 128, 130 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species or invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 10/21/2003.

Claims 77-97, 104-106, 110, 117-122, 124, and 127-132 are being examined to the extent that they read upon the elected species.

The application is not fully in compliance the sequence rules, 37 C.F.R. § 1.821-1.825. The specification fails to recite the appropriate sequence identifiers at each place where a sequence is discussed. See pages 37, 43, Figures-3a, -3b. This is not meant to be an exhaustive list of places where the specification fails to recite the appropriate sequence identifiers. The application cannot issue until it is in compliance. Nucleic acid sequences with 10 or more nucleotides, at least 4 of which are specifically defined, must comply with the sequence rules. Amino acid sequences with 4 or more residues, at least 4 of which are specifically defined, must comply with the sequence rules. Applicant may bring the Figures into compliance by amending either the Figures or the "Brief Description of the Drawings" to recite the appropriate sequence identifier. Applicants' amendment filed 07/20/00 (Paper No. 13) is noted. However, the sequence listing does not contain a "SEQ ID NO: 339737". Furthermore, the amino acid sequence (Figure 3b) and the nucleotide sequence (Figure 3a) require separate identifiers.

Correction is required.

Claim Rejections - 35 USC § 103

Claims 77-81, 85, 87-91, 104-106, 110, 117-122, 124, 129, 131, 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mouritsen (AV, cited by Applicants) in view of {Pennica (BP, cited by Applicants), Shirai (BN, cited by Applicants), or Wang (BL, cited by Applicants)}, further in view of Jones (BF, cited by Applicants), and further in view of Panina-Bordigon (BO, cited by Applicants).

Mouritsen teaches a modified mouse TNFα molecules wherein at least one peptide fragment of the mouse TNFα molecule has been substituted by at least one peptide known to contain an immunodominant T cell epitope wherein the substitution introduces a substantial change in the amino acid sequence of the B strand of the front β-sheet (page 10, line 8, through page 11, line 12). Substitutions in this region detoxify the recombinant protein (page 12, lines 16-17). Toxic self proteins such as TNFα can be simultaneously detoxified by removing or mutating biologically active protein segments (page 7, lines 11-15). The modified TNFα could be administered as an anti-TNFα vaccine to patients suffering from diseases where TNFα is important for the pathogenesis (page 14, lines 13-20, 26-30; paragraph bridging pages 14-15). Mouritsen teaches the modified TNFα may be prepared as a fusion protein with GM-CSF or interleukin 2 (page 7, full paragraph 2; paragraph bridging pages 9-10). Mouritsen teaches T cell epitopes derived from tetanus toxin (page 14, line 15). The native form of TNFα is known to be a trimer. Mouritsen describes DNA molecules encoding the modified TNFα molecule, expression vectors comprising the DNA molecules, host cells comprising the vectors, and a recombinant method of producing the modified TNFα molecules (page 8, line 10, through page 9, line 6; page 10, line 8, through page 11, line 12; page 14, lines 13-20; Figure 3). Mouritsen teaches a vaccine against TNFα comprising the modified TNFα molecule and calcium phosphate (page 7, full paragraph 2), and injection of the vaccine (page 7, paragraph bridging pages 6-7).

Mouritsen (AV) clearly teaches that injection of recombinant proteins, which have been appropriately modified by the insertion of foreign T cell epitopes, induces an autoantibody response against the recombinant protein. By using this principle for

developing vaccines against undesirable proteins, the risk of inducing allergic side-reactions is reduced, and toxic self proteins can simultaneously be detoxified by removing or mutating biologically active segments (page 6, line 29, through page 7, line 15). Furthermore, Mouritsen (AV) clearly teaches the induction of anti-TNF antibodies in order to affect TNF-mediated diseases (page 14, lines 26-30), which provides a motivation, teaching and guidance to produce TNF neutralizing anti-TNF antibodies. There is a clear motivation, teaching, and suggestion in Mouritsen (AV), taken as a whole, to modify TNF so that neutralizing antibodies to TNF could be raised. The success of Mouritsen (AV) in raising antibodies to mouse TNF provides a reasonable expectation of success that antibodies to other TNFs could be raised. Mouritsen (AV) also provides the motivation to select those antibodies that neutralize TNF. Namely, the modified TNF could be administered as an anti-TNFα vaccine to individuals suffering from diseases where TNFα is important for the pathogenesis. Mouritsen (AV) also provides an assay for the measurement of TNF bioactivity. Specifically, the L929 bioassay for TNFα (page 12, lines 16-17). It would require no more than routine experimentation for one of ordinary skill in the art to make modified murine TNF molecules, raise antibodies to such modified TNFs, and screen those antibodies for neutralization of TNF biological activity, in the L929 bioassay for TNFα. It is obvious from the disclosure of Mouritsen (AV) that it is necessary to make modified TNF molecules that are devoid of significant biological activity and at the same time are capable of raising neutralizing antibodies to unmodified TNF.

Mouritsen does not teach a modified human TNFα molecule in the same sense that Mouritsen does not anticipate the pending claims. Pennica (Figure 1), Shirai (Figure

1), or Wang (Figure 4) teach human TNFα molecules and DNA molecules encoding same. Pennica, Shirai, or Wang do not teach a modified human TNFα molecule for use as a vaccine. However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention make a modified mouse TNFα molecule, as taught by Mouritsen, and to modify that teaching by substituting a human TNFα molecule, as taught by Pennica, or Shirai, or Wang, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because the human protein could be administered as an anti-TNFα vaccine to humans suffering from diseases where TNFα is important for the pathogenesis.

Mouritsen in view of Pennica, Shirai, or Wang do not teach a substitution in the E/F connecting loop.

Jones teaches: the highly flexible loop regions form potential linear epitopes prominently displayed on the surface of the native TNF structure (paragraph bridging pages 109 and 113); the interaction between TNF and its receptor must somehow differ from those required for binding of an antibody to TNF (page 113, full paragraphs 1-2); regions of functional importance for receptor binding (paragraph bridging pages 113-114 through paragraph bridging pages 122 and 124, and the tables and figures therein); the E strand, the E/F connecting loop, and F strand comprise amino acids 76-83, 84-90, and 91-98, respectively (Figure 4); mutations in amino acids 84, 86, 87 abrogate biological activity (Figure 13; Tables 2 and 4). Jones does not teach substituting the E/F connecting loop with an immunodominant T cell epitope.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a modified human TNFα molecule, as taught by

Mouritsen in view of Pennica, Shirai, or Wang, and to modify that teaching by substituting a region comprising amino acids 84, 86, or 87 with an immunodominant T cell epitope, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this substitution in these regions because such substitutions would detoxify the recombinant protein.

Mouritsen in view of Pennica, Shirai, or Wang further in view of Jones do not teach substituting a region comprising amino acids 84, 86, or 87 of human TNFα with p2 or p30 epitopes.

Panina-Bordigon teaches: p2 (15 amino acids) and p30 (21 amino acids) epitopes (page 2238, column 1, full paragraph 1); these epitopes are universally immunogenic and can be recognized in association with a large number of class II molecules (page 2237, column 2, full paragraph 1; page 2238, column 2, full paragraph 3); the fact that p2 and p30 epitopes show a very promiscuous binding to human class II molecules is encouraging for the development of synthetic vaccines that will be active in a large portion of the population (page 2241, paragraph bridging columns 1-2). Panina-Bordigon does not teach a modified human TNFα molecule comprising p2 or p30 epitopes.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a modified human TNFα molecule, as taught by Mouritsen in view of Pennica, Shirai, or Wang, and further in view of Jones, and to modify that teaching by substituting the p2 and/or p30 epitopes, as taught by Panina-Bordigon, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification because p2 and p30 epitopes show a very promiscuous binding to human class II molecules and such binding is encouraging for the

development of synthetic vaccines that will be active in a large portion of the population. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to make a p2 (15 amino acids) and p30 (21 amino acids) substitution centered on a region of functional importance in the human TNFα molecule, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this substitution because substitutions in these regions would detoxify the recombinant protein.

A 15 amino acid substitution, such as with p2, or a 21 amino acid substitution, such as with p30, at amino acids 84, 86, or 87 would encompass a substitution in the D/E connecting loop, the E strand, and the E/F connecting loop, a substitution of in the E strand and in the E/F connecting loop, a substitution in the E strand, the E/F connecting loop, and the F strand, or a substitution in the E/F connecting loop and in the F strand. Since all of the claimed species of substitutions cannot all be non-obvious, the examiner considers them obvious.

Furthermore, Jones clearly indicates regions in TNF of functional importance for biological activity (paragraph bridging pages 113-114 through paragraph bridging pages 122 and 124, and the tables and figures therein). Jones (BF) also teaches a putative receptor binding site involving residues 11 to 13, 37 to 42, 49 to 57, and 155 to 157 and mutations in amino acid residues that abrogate TNFα activity (Jones, Tables 2 and 3). It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to substitute the p2 (15 amino acids) and p30 (21 amino acids) such that the insertion occurred in the region 11 to 13, 37 to 42, 49 to 57, and 155 to 157. Substitution of a region comprising 49 to 57 or a portion thereof with p2 or p30 would involve a

segment of the D strand of the back β sheet. Substitution of amino acid 143, 146, 147, or 148 (mutations that abrogate biological activity, see Jones, Figure 13) or a portion of a region comprising amino acids 143, 146, 147, or 148 with p2 or p30 would be a substitution that comprises at least a segment of the H strand of the front β sheet and of the connecting loop to the I strand, or segments of the H and I strands and the entire connecting loop. The loop connecting the D and E strands comprises amino acids 68 to 75. It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to substitute the loop connecting the D and E strands with p2 or p30 with a reasonable expectation of success. One of ordinary skill in the art would be motivated to make this modification in order to abrogate TNFα activity. Such a substitution would comprise a segment of the D strand, at least a segment of the E strand and the entire connecting loop. Substitution of the loop connecting the D and E strands with p2 or 30 would comprises substitution of amino acids 65 to 79. Substitution of amino acids 37 to 42 or 49 to 57 with p2 or p30 would comprise substitution of the entire C' and C strands and a segment of the D strand or comprise substitution of amino acids 40 to 60. Such a substitution would comprise at least a segment of the E strand (amino acids 76-83) and of one or both of the connecting loops (amino acids 68-75 or 84-90), or comprise amino acids 76 to 90. SEQ ID NOs: 4, 8, and 10 comprises substitutions of amino acids 66-80, 133-147, and 77-91, respectively, with p2. SEQ ID NOs: 14, 16, and 20 comprise substitution of amino acid residues 41-61, 65-85, and 132-152, respectively, with p30. Each of amino acid residues 66-80, 133-147, 77-91, 41-61, 65-85, and 132-152 comprise regions that abrogate or substantially reduce TNFα bioactivity. See Jones, Tables 2 and 3, and Figures 13 and 14.

TNFα is a 157 amino acid molecule. At first glance, the regions substituted in claim 77 encompass the entire molecule except for amino acids 1-18 and amino acids 113-126. However, there is some uncertainty in how to construe the claims. It is unclear if the substitutions only encompass the specifically recited regions or if the substitutions encompass at least a part of the specifically recited regions. In the latter case, substitution with a 15 amino acid immunodominant T cell epitope, such as p2, would mean that essentially anywhere in the entire TNFα could potentially be substituted except for four amino acids at the amino terminus. Also in the latter case, substitution with a 21 amino acid immunodominant T cell epitope, such as p30, would mean that essentially anywhere in the entire TNFα could potentially be substituted. The cited prior art clearly suggest substitution of an immunodominant T cell epitope into human TNFα.

It would have been obvious to one of ordinary skill in the art at the time of Applicants' invention that, although one could immunize against TNF-α, unless the antibodies produced were neutralizing antibodies then vaccinating against TNF-α would serve no purpose. The prior art of Jones recognizes that there are neutralizing and non-neutralizing TNF-α antibodies and one of ordinary skill in the art would be motivated to select for neutralizing antibodies because the generation of neutralizing antibodies would provide an efficacious vaccine, whereas non-neutralizing antibodies would not. Furthermore, the prior are recognizes that an antibody binding TNF-α sufficiently close to a putative TNF-α receptor binding site blocks the receptor binding.

The prior art provides the requisite motivation to select between working analogs and non-working analogs and guides one of ordinary skill in the art to select for the proper sites for substitution. Although immunogenicity is required for vaccination,

immunogenicity, in the absence of neutralization, is not sufficient for vaccination because non- neutralizing antibodies would not block TNF-α biological activity and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to select for those immunization reagents and procedures that produce neutralizing antibodies. In view of the combined teachings of the prior art the teachings of the instant application cannot be considered as surprising and unexpected.

It would have been further obvious to one of ordinary skill in the art to make fragment of human TNFα comprising a T-cell epitope because smaller peptides would require much smaller net amounts on a mole per mole basis for administration than the intact molecule. Smaller peptides could be synthesized easily using simple peptide chemistry procedures. The invention is prima facie obvious over the prior art.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Applicant argues that Mouritsen does not teach where to introduce the foreign epitope, or that there might be preferred parts for the insertion. Applicant's arguments have been fully considered but they are not persuasive. The prior art provides the

requisite motivation to select between working analogs and non-working analogs and guides one of ordinary skill in the art to select for the proper sites for substitution.

Applicant argues that Mouritsen does not teach where the biologically active segments are located, how they could be identified, or how they should modified. Applicant's arguments have been fully considered but they are not persuasive. The prior art provides the requisite motivation to select between working analogs and non-working analogs and guides one of ordinary skill in the art to select for the proper sites for substitution.

Applicant argues that Mouritsen teaches that T-cell epitopes might be used without any support for the usability of such epitopes. Applicant's arguments have been fully considered but they are not persuasive. Applicant has not presented any objective evidence suggesting the un-usability of such epitopes. The arguments of counsel cannot take the place of evidence in the record. Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding inoperability of the prior art.

Applicants argue that MR105 is the most attractive -- or only possible -- modification suggested by Mouritsen because MR103 and MR106 would leave the skilled artisan with the additional problem of looking for targets for detoxifying TNFα. Applicant's arguments have been fully considered but they are not persuasive. This argument presumes that MR103 and MR106 are biologically active. However, no evidence has been presented that MR103 and MR106 are biologically active. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, claimed

properties or functions are presumed to be inherent, and a prima facie case of either anticipation or obviousness has been established. TNFα is a 157 amino acid molecule. At first glance, the regions substituted in claim 77 encompass the entire molecule except for amino acids 1-18 and amino acids 113-126. However, there is some uncertainty in how to construe the claims. It is unclear if the substitutions only encompass the specifically recited regions or if the substitutions encompass at least a part of the specifically recited regions. In the latter case, substitution with a 15 amino acid immunodominant T cell epitope, such as p2, would mean that essentially anywhere in the entire TNFα could potentially be substituted except for four amino acids at the amino terminus. Also in the latter case, substitution with a 21 amino acid immunodominant T cell epitope, such as p30, would mean that essentially anywhere in the entire TNFα could potentially be substituted. Burden is shifted to Applicant to distinguish between the human TNFα substitution suggested by Mouritsen's MR103, MR106, and the presently claimed invention.

Applicant's arguments regarding the result being a long way from given, minimally obscuring the tertiary structure, and expectations when using other T cell epitopes is acknowledged. However, the arguments of counsel cannot take the place of evidence in the record. Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding inoperability of the prior art. Furthermore, Panina-Bordigon teach: p2 (15 amino acids) and p30 (21 amino acids) epitopes (page 2238, column 1, full paragraph 1); these epitopes are universally immunogenic and can be recognized in association with a large number of class II molecules (page 2237, column 2, full paragraph 1; page 2238,

column 2, full paragraph 3); the fact that p2 and p30 epitopes show a very promiscuous binding to human class II molecules is encouraging for the development of synthetic vaccines that will be active in a large portion of the population (page 2241, paragraph bridging columns 1-2). Applicant has presented no evidence to the contrary.

The examiner does not agree that MR105 is "the only specific teaching one might deduce from Mouritsen." Nor does Mouritsen MR105 mutant vitiate the teachings, suggestions and motivations, found in the prior art. Application of impermissible "obvious to try" standard usually occurs when invention is made by varying all parameters or trying each of numerous choices until successful without indication in prior art as to which parameters were critical or which choices were likely to be successful, or when invention is made by exploring promising new technology or general approach with only general guidance from prior art as to particular form of claimed invention or how to achieve it. The prior art provides the requisite motivation to select between working analogs and non-working analogs and guides one of ordinary skill in the art to select for the proper sites for substitution.

Applicant argues that the present invention shows how important it is to select segments to be modified. Applicant's arguments have been fully considered but they are not persuasive. The present claims require that the modified TNFα be biologically inactive and that it be capable of raising neutralizing antibodies. Both of these limitations are adequately taught or suggested by the prior art.

Applicant argues that Mouritsen does not teach the existence of individual differences in different self-antibodies. Applicant's arguments have been fully considered but they are not persuasive. It seems obvious that one of ordinary skill in the art would

reasonably expect there to be differences in different self-antibodies. One of ordinary skill in the art would not reasonably expect all non-neutralizing antibodies to be identical. One of ordinary skill in the art would not reasonably expect all neutralizing antibodies to be identical. The important point is to select for those TNFα mutants that are biologically inactive and capable of raising neutralizing antibodies. Both of these limitations are adequately taught or suggested by the prior art. Patentability requires novelty and unobviousness in light of the prior art, not in light of what the inventor knew and included in his patent application.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Response to arguments filed May 2, 2003 - "SUPPLEMENT TO AMENDMENT"

Applicant argues that Mouritsen (WO 95/05849) does not teach or suggest the induction of neutralizing antibodies. The prior art provides the requisite motivation to select between working analogs and non-working analogs and guides one of ordinary skill in the art to select for the proper sites for substitution. Although immunogenicity is required for vaccination, immunogenicity, in the absence of neutralization, is not sufficient for vaccination because non- neutralizing antibodies would not block TNF-α

biological activity and it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to select for those immunization reagents and procedures that produce neutralizing antibodies.

Applicant argues that following the teachings of Mouritsen one skilled in the art would end up with a modified human TNFα, such as TNF2-1, but that TNF2-1, the modified human TNFα following from the teachings of Mouritsen, does not induce antibodies with a neutralizing effect. Therefore, the teachings of Mouritsen would not have lead one skilled in the art to produce claimed TNFα. Applicant's arguments have been fully considered but they are not persuasive. This argument presumes that MR103 and MR106 are biologically active. However, no evidence has been presented that MR103 and MR106 are biologically active. Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, claimed properties or functions are presumed to be inherent, and a prima facie case of either anticipation or obviousness has been established. TNFα is a 157 amino acid molecule. At first glance, the regions substituted in claim 77 encompass the entire molecule except for amino acids 1-18 and amino acids 113-126. However, there is some uncertainty in how to construe the claims. It is unclear if the substitutions only encompass the specifically recited regions or if the substitutions encompass at least a part of the specifically recited regions. In the latter case, substitution with a 15 amino acid immunodominant T cell epitope, such as p2, would mean that essentially anywhere in the entire TNFα could potentially be substituted except for four amino acids at the amino terminus. Also in the latter case, substitution with a 21 amino acid immunodominant T cell epitope, such as p30, would mean that

essentially anywhere in the entire TNFα could potentially be substituted. Burden is shifted to Applicant to distinguish between the human TNFα substitution suggested by Mouritsen's MR103, MR106, and the presently claimed invention.

Applicant argues that in Mouritsen it is neither disclosed nor suggested to modify TNFα in parts of the molecule, such that biologically inactive TNFα may be used to induce neutralizing anti-TNFα antibodies. Applicant's arguments have been fully considered but they are not persuasive. Mouritsen clearly suggest neutralizing TNFα biological activity by modifying the TNFα by insertion of a T-cell epitope (page 7, full paragraph 1). One of ordinary skill in the art knows that highly potent inhibiting and/or neutralizing anti-TNF antibodies are preferred for therapeutic use in TNFα-mediated pathologies or conditions. See 5656272 Le (A), column 9, lines 45-50; paragraph bridging columns 48-49.

Applicant argues that the claimed invention shows that it is very important to select the segments to be modified. Applicant's arguments have been fully considered but they are not persuasive. TNFα is a 157 amino acid molecule. At first glance, the regions substituted in claim 77 encompass the entire molecule except for amino acids 1-18 and amino acids 113-126. However, there is some uncertainty in how to construe the claims. It is unclear if the substitutions only encompass the specifically recited regions or if the substitutions encompass at least a part of the specifically recited regions. In the latter case, substitution with a 15 amino acid immunodominant T cell epitope, such as p2, would mean that essentially anywhere in the entire TNFα could potentially be substituted except for four amino acids at the amino terminus. Also in the latter case, substitution with a 21 amino acid immunodominant T cell epitope, such as p30, would mean that

essentially anywhere in the entire TNFα could potentially be substituted. One of ordinary skill in the art would be motivated to select a modification of TNFα that gives rise to neutralizing anti-TNFα antibodies because neutralizing anti-TNFα antibodies would be expected to be an effective treatment for TNFα-mediated conditions.

New Formal Matters, Objections, and/or Rejections:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 77-97, 104-106, 110, 117-122, 124, and 127-132 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 77-97, 104-106, 110, 117-122, 124, and 127-132 recited the limitation "said modified TNFα" (claim 77, line 2). There is a lack of antecedent basis for this limitation in the claims.

Claims 90, 91, 132 are indefinite over the recitation of "known to be" (claim 90) because it is unclear what person, thing or entity is supposed to possess such knowledge and when such person, thing or entity is supposed to possess such knowledge. The metes and bounds are not clearly set forth.

Claims 91, 132 are indefinite over the recitation of "derived from" because the nature and the extent of the derivation are unclear. The metes and bounds are not clearly set forth.

Claim Objections

Claim 89 is objected to because of the following informalities: "or the to the" doesn't make any sense. Appropriate correction is required.

Conclusion

No claims are allowed.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (571) 272-0887.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

BEFORE FINAL (703) 872-9306
AFTER FINAL (703) 872-9307

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (571) 273-0890.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
FEBRUARY 19, 2004